

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents lists available at ScienceDirect

# Clinical Imaging

journal homepage: www.elsevier.com/locate/clinimag





# QIBA guidance: Computed tomography imaging for COVID-19 quantitative imaging applications

Ricardo S. Avila <sup>a,\*</sup>, Sean B. Fain <sup>b</sup>, Chuck Hatt <sup>c,p</sup>, Samuel G. Armato III <sup>d</sup>, James L. Mulshine <sup>e</sup>, David Gierada <sup>f</sup>, Mario Silva <sup>g</sup>, David A. Lynch <sup>h</sup>, Eric A. Hoffman <sup>i</sup>, Frank N. Ranallo <sup>j</sup>, John R. Mayo <sup>k,q</sup>, David Yankelevitz <sup>l</sup>, Raul San Jose Estepar <sup>m,r</sup>, Raja Subramaniam <sup>l</sup>, Claudia I. Henschke <sup>l</sup>, Alex Guimaraes <sup>n</sup>, Daniel C. Sullivan <sup>o</sup>

- <sup>a</sup> Accumetra, LLC, United States of America
- <sup>b</sup> University of Wisconsin Madison, United States of America
- <sup>c</sup> Imbio, LLC, United States of America
- <sup>d</sup> University of Chicago, United States of America
- <sup>e</sup> Rush University, United States of America
- f Washington University, United States of America
- g University of Parma, Italy
- <sup>h</sup> National Jewish Health, United States of America
- i University of Iowa, United States of America
- <sup>j</sup> University of Wisconsin, United States of America
- <sup>k</sup> Vancouver General Hospital, Canada
- <sup>1</sup> Mount Sinai Health System, United States of America
- m Brigham and Women's Hospital, United States of America
- <sup>n</sup> Oregon Health & Science University, United States of America
- <sup>o</sup> Duke University, United States of America
- <sup>p</sup> University of Michigan, United States of America
- <sup>q</sup> The University of British Columbia, Canada
- <sup>r</sup> Harvard Medical School, United States of America

#### ARTICLE INFO

Keywords: COVID-19 Quantitative imaging Artificial intelligence Computed tomography

#### ABSTRACT

As the COVID-19 pandemic impacts global populations, computed tomography (CT) lung imaging is being used in many countries to help manage patient care as well as to rapidly identify potentially useful quantitative COVID-19 CT imaging biomarkers. Quantitative COVID-19 CT imaging applications, typically based on computer vision modeling and artificial intelligence algorithms, include the potential for better methods to assess COVID-19 extent and severity, assist with differential diagnosis of COVID-19 versus other respiratory conditions, and predict disease trajectory. To help accelerate the development of robust quantitative imaging algorithms and tools, it is critical that CT imaging is obtained following best practices of the quantitative lung CT imaging community. Toward this end, the Radiological Society of North America's (RSNA) Quantitative Imaging Biomarkers Alliance (QIBA) CT Lung Density Profile Committee and CT Small Lung Nodule Profile Committee developed a set of best practices to guide clinical sites using quantitative imaging solutions and to accelerate the international development of quantitative CT algorithms for COVID-19. This guidance document provides quantitative CT lung imaging recommended CT image acquisition settings for contemporary CT scanners. Additional best practice guidance is provided on scientific publication reporting of quantitative CT imaging methods and the importance of contributing COVID-19 CT imaging datasets to open science research databases.

E-mail address: rick.avila@accumetra.com (R.S. Avila).

<sup>\*</sup> Corresponding author.

#### 1. Introduction

The world has experienced three coronavirus outbreaks in the past two decades, with a prospect for increasing frequency and virulence in the future related to growing population densities, increased urbanization, and expansion of industrial activity. At the time of this writing, the World Health Organization reported over 98 million confirmed COVID-19 cases and over 2 million confirmed deaths worldwide. The growing toll in human life and economic costs of this pandemic demand the full attention of the clinical and research communities. While therapies for COVID-19 have been made available they are not fully curative, and most of the world population is not immune to the virus, thus research into more effective disease management methods, including the optimal application of CT imaging, remains a high priority.

Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of samples from nasopharyngeal swabs represents the current standard of care. <sup>2,3</sup> However, poor sensitivity and specificity of RT-PCR and CXR at the early stages of COVID-19, and especially in the setting of limited availability or equivocal results, 4 reduce effectiveness to identify and isolate COVID-19 disease early in patient management. In some settings, CT imaging has been deployed as an alternative diagnostic approach, and in some countries continues to be standard of care. 5 Several recent studies have reported a higher diagnostic sensitivity for CT compared with RT-PCR<sup>6–8</sup> and CXR<sup>9</sup>; however, use of CT has been discouraged for general population COVID-19 diagnosis in many countries because of concerns that include low specificity, limited scanner availability, and the potential for contamination of the scanner environment. 10-1 Nevertheless, investigations into quantitative CT for COVID-19 continue to show promise and the applicability of CT in COVID-19 diagnosis remains an active area of research.

Chest CT imaging also represents a potentially important tool in the management of COVID-19 patients. Chest CT has several characteristic findings, particularly in the acute phase of COVID-19, including groundglass opacities with a predominantly peripheral and basilar distribution; however, there can be uncommon findings associated, such as pleural effusions or lymphadenopathy, as well as other superimposed conditions, such as other pneumonias or edema. Despite this complexity, the CT image features of COVID-19 are sometimes distinguishable from other types of viral pneumonia. 5,13,14 In the early stages of COVID-19, the predominant CT finding is focal rounded ground-glass lesions in the posterior lower lungs, with increasing consolidation observed during disease progression. 15-19 Such imaging features of lung infection progression on CT scans may be prognostic for more severe acute disease. 19 Visual scoring methods for detecting and assessing the severity of COVID-19 have been developed<sup>20–22</sup> and there are now standard lexicons for how CT findings should be reported <sup>23,24</sup> and also descriptions of the change in CT findings over time.2

Although radiologist visual scoring systems have been developed,<sup>20</sup> these only provide gross estimations of the extent of disease. More valuable clinical information may be elucidated through more advanced CT image processing to more objectively characterize disease status. For example, several promising deep learning-based<sup>25</sup> diagnostic classifiers have emerged using data from China<sup>26-31</sup> where experience with the disease began in December 2019. Chest CT was utilized more frequently in China, including with less severe cases, as they were first studying this disease. 21,23 In addition, several studies have reported change in CT findings with COVID-19 over time<sup>17,32,33</sup> including one study suggesting that quantitative CT may contribute to prognosis by predicting future rate of disease progression.<sup>34</sup> With regard to pulmonary vasculature, a recent study reported a measurable impact of vasoconstriction of the small vessels leading to vasodilation of medium-sized vessels in COVID-19 patients. Quantification of these changes is measurable on CT and may be useful to guide specific targeted drug interventions. 13,18 Assessing this type of measurable change in small vessel diameter would require precise, consistent performance with the CT imaging process. Recently, the use of quantitative CT as an adjunct to RT-PCR in the

diagnosis of COVID-19 has been shown to improve early detection. <sup>35</sup> As these promising quantitative CT applications are investigated, it is important to recognize that the ability of quantitative image analysis and/or machine learning techniques to serve as accurate diagnostic and/or prognostic tools for COVID-19 assessment will depend on the quality and consistency of the CT imaging data in conjunction with curation of accurate information on patient presentation, timing of disease progression, and patient outcome.

To achieve consistent CT image-based measurements of early disease changes to guide clinical management, the importance of standardization of scanning protocols for these indications cannot be overstated. Reducing variability in dose, pitch, and scanning time in addition to minimizing respiratory motion will improve the diagnostic accuracy, predictability, and utilization of CT scanning in this disease. Scanning protocols will have to meet regional standards of quality and will need to incorporate additional considerations to account for the peculiar limitations encountered in patients with respiratory symptoms. Challenging respiratory symptoms such as shortness of breath are frequently present in patients referred for imaging during the COVID-19 pandemic. Proper choice of CT image acquisition protocol can minimize motion artifacts while maintaining high image quality in a patient who is experiencing a rapid breathing rate. Such high image quality will support improved image interpretation and precision of computer measurement of image features

Ideally, CT datasets should be composed of images with consistent quality to allow for the best quantitative analyses of the diffuse parenchymal abnormalities that frequently overlap in COVID-19 pneumonia. Radiological features frequently observed with COVID-19 pneumonias include ground-glass opacities and different types of consolidation (e.g., active inflammation, dependent atelectasis), either as isolated findings or as mixed components with variable overlap among them. Image acquisition protocols should aim to achieve consistent morphological display and quantitative data throughout the density range of these findings.

In this document, the QIBA CT Lung Density and CT Small Lung Nodule Profile subcommittees<sup>36</sup> suggest best practice methods and CT image acquisition parameters to support optimal ongoing and future quantitative analysis of COVID-19. We are making provisional recommendations to facilitate the collection of CT images with sufficient quality to enable development and validation of quantitative imaging and machine learning methods for this new lung disease. These recommendations, in part, are designed to mitigate motion artifacts, establish minimum spatial resolution standards (for example, for slice thickness), and disseminate preferred reconstruction algorithms. The intent of this guidance document is to standardize quantitative imaging protocols in the clinical care setting, to improve the collection of imaging data for quantitative imaging research studies, and to support development of more precise imaging biomarkers to diagnose and provide quantitative outcome measures to assess new therapies.

# 2. Imaging guidance

Whether applying quantitative CT imaging algorithms in a clinical care setting or developing new quantitative algorithms in a research setting, the choice of image acquisition and reconstruction parameters can have a large impact on the resulting measurements. This guidance suggests parameter selection for COVID-19 CT imaging algorithms designed to collect high-quality imaging data in the clinical care setting and help clinical imaging sites reliably use quantitative CT imaging results. In emergency situations as reported in the early stages of the COVID-19 pandemic, conforming with optimal guidelines may not be possible; however, clinical care personnel should be aware that higher levels of variability and error are likely to be present when lower quality CT images are used for quantitative purposes. Some deviations from the recommended protocols can yield images unsuitable for quantitative analysis. While the recommendations have not yet been rigorously

clinically validated, they are based on large numbers of CT lung imaging studies and CT lung imaging consensus over the last decade and represent the most reliable guidance information available.

A review of initial COVID-19 quantitative CT imaging publications and areas of active research indicates three main settings for which quantitative algorithms are currently being developed:

- 1) Assessment of extent and severity of COVID-19 radiological features.
- Differential diagnosis of COVID-19 versus other respiratory conditions.
- 3) Prediction of disease course trajectory.

Algorithms that perform these analyses must successfully identify the lung boundaries in a full anatomic extent lung CT scan and correctly classify, delineate, and evaluate properties of lung regions that demonstrate manifestations of COVID-19. This will allow for the extraction of quantitative information such as the volume (percent) of affected lung lobes impacted by consolidation or more diffuse inflammation (presenting as ground glass or ground glass – reticular opacities). In addition, regions of hyperlucency may provide an indication of microemboli, hypoxic vasoconstriction, or hyper-inflation associated with peripheral airway inflammation. Assessment of subtle lung density changes, are especially relevant as they may indicate early disease. While peripheral small airways involvement has been assessed on expiratory images as air-trapping or through matching of fullinspiratory to full-expiratory scans, <sup>37,38</sup> in the setting of COVID-19, expiratory scans are not currently being advocated. Radiologic changes due to COVID-19 may be present concurrent with many other comorbid conditions with overlapping radiological characteristics including asthma, COPD, interstitial lung disease (ILD), pulmonary hypertension, and lung cancer. Because of this, it is important that quantitative algorithms operate on CT images with accurate Hounsfield Unit (HU) values, good low-contrast detectability performance, and high three-dimensional resolution so that subtle features specifically associated with COVID-19 can be distinguished from features associated with other diseases.

For meaningful quantification, it is very important that patients be coached to full inspiration (total lung capacity) and remain apneic and immobile during the time of scanning (or mechanical ventilation be temporarily suspended). If an expiratory scan is necessary, it is important to coach the patient to full expiration (residual volume). Density-based quantitative CT requires that the scan be performed without contrast agent. If additional scanning requires contrast agent, the scan for quantitative assessment of the lung parenchyma should be performed first so that there is no contrast agent circulating at the time of imaging.

The following guidance on CT image acquisition parameters has been shown to achieve high-quality results for quantitative CT lung imaging algorithms including those for measuring lung density<sup>39,40</sup> and volumetric size changes for small sub-centimeter lung nodules. 41-44 Additional guidance on CT quantitative lung imaging protocols are available publicly on the QIBA wiki pages (http://qibawiki.rsna.org/index.php/Lung\_Density\_Biomarker\_Ctte and http://qibawiki.rsna.org/index.php/CT\_Small\_Lung\_Nodule\_Biomarker\_Ctte).

#### 2.1. Lung inflation

Segmentation and classification of structures (e.g., nodules) and/or tissue types (e.g., pneumonia, emphysema) is dependent on the HU distributions within the lungs, which in turn are affected by the amount of air in the lungs. Because of this, controlling for lung inflation volume is critical for achieving meaningful and repeatable quantification. Specifically, scanning at full inspiration should be encouraged. A coaching protocol that has worked well in quantitative CT settings is the following <sup>39</sup>:

- "Take a deep breath in" (watch the chest to ensure deep inspiration is achieved)
- "Let it out" (watch chest to ensure exhale is achieved)
- "Take a deep breath in" (watch the chest to ensure exhale is achieved and timing of breath cycle for the patient)
- "Let it out"
- "Now breathe all the way IN, IN, IN..." (watch to confirm timing and inhalation is fully achieved and chest is still)
- "Keep holding your breath DO NOT BREATHE"
- Visually confirm inspiratory breath-hold by watching patient's chest and commence CT scan.
- "Breathe and Relax."

#### 2.2. Contrast agent

The presence of contrast agent introduces a temporally and spatially varying shift in the HU distribution of the lungs, which can adversely affect segmentation, texture analysis, tissue classification, and measurement performance. However, use of intravenous contrast agent is often warranted, such as for CT angiography and many abdominopelvic imaging indications, after appropriate consideration of risks and benefits. If a contrast agent is prescribed, and if quantification is desired, then we recommend performing a non-contrast agent scan before the contrast-agent scan. <sup>45</sup> Care should be taken when deciding to administer contrast agent, as renal toxicity is a concern for many high-risk COVID-19 patients.

#### 2.3. Pitch

For patient motion considerations, breath-hold time should ideally be minimized to <5 s to improve patient adherence and decrease the likelihood of motion artifacts in dyspneic patients undergoing CT for suspected or confirmed COVID-19 pneumonia. Depending on scanner architecture, rotation time can be reduced to 0.25 s/cycle for 64-detector scanners or greater, or typically 0.4 to 0.5 s/cycle for 16 or fewer detectors. A pitch of approximately 1 is recommended for 64-detector scanners or greater to minimize helical artifact, whereas a pitch of 1.3 or greater is necessary for conventional single-source scanners with 16 or fewer detectors to achieve sufficiently short scan times. Dual or multiple-source scanners will allow the fastest acquisition time with pitch up to 3.4, but substantially lower pitches (<2) are recommended to reduce helical artifact assuming a <5 s scan time can be achieved.

#### 2.4. Table feed direction

Setting the table feed direction to caudo-cranial can reduce the likelihood and/or magnitude of motion artifacts due to respiration. Selective timing of anatomic coverage of the lung regions, which exhibit a different range of motion over the z-axis, is indeed paramount. If high respiratory motion is expected, a CT acquisition starting near the location of greatest motion is recommended. Lung bases are characterized by substantial motion during the respiratory cycle, which is quite unpredictable in the case of COVID-19 pneumonia. On the other hand, z-axis motion is extremely limited in the lung apices throughout the respiratory cycle, and minor motion artifacts in this region might have a less detrimental effect on the quality of data for quantitative assessment. Therefore, the lung bases should be scanned first with the aim of acquiring this region within the first second of breath hold. This approach might be particularly helpful when using scanners with fewer detector rows.

# 2.5. Collimation

The use of a large collimation setting has the potential to cause variability in reconstructed HU values. To reduce this, it is recommended to restrict field collimation to  $<\!80$  mm.

#### 2.6. Slice thickness and spacing

Slice thickness has a large impact on the three-dimensional resolution within a CT scan. It is therefore recommended to use  $\leq 1.25$ -mm CT slice thickness for COVID-19 imaging studies. To avoid gaps in collected image data, slice spacing (reconstruction interval) should be no greater than slice thickness to prevent slice gaps and not less than half slice thickness to mitigate axial interpolation error.

#### 2.7. Radiation dose

CT imaging is being used and investigated for a range of quantitative COVID-19 applications including measurement of baseline disease extent, where standard chest CT dose is recommended, and measurement of disease extent to assess resolution by conducting follow-up CT scans, where lower doses may be warranted. Each CT application scenario will require different levels of emphasis on lowering radiation dose. In this guidance we provide recommendations for lowering radiation dose when needed, recognizing that standard dose CT chest imaging is predominantly performed.

Given that one of the major findings on CT is ground glass opacities of varying attenuation, some with evidence of crazy-paving and consolidation, low-dose scans that have increased amounts of noise may not be appropriate as these low-contrast lesions are most affected. Noise reduction can be achieved using higher voltage than typically used in screening exams. When clinical care indicates that a lower radiation is appropriate, it is recommended that radiation dose be consistent with the recommendations in the QIBA Lung Density Profile, <sup>39</sup> which states that CTDIvol be targeted to 3 mGy for an average-sized patient (i.e., 75 kg) with the amount of radiation adjusted based on patient size and shape according to the scanner manufacturer.

Automated exposure control (AEC) should be used to reduce dose and make noise behavior more consistent throughout the image. Although different vendors use proprietary AEC techniques, CT radiation dose in the chest is expected to vary by  $\pm 18\%$  for subject weight between 50 and 100 kg,  $^{39}$  which is considered sufficiently small to maintain the expected performance of quantitative analysis techniques.

The use of iterative reconstruction (IR) is desirable to reduce CT dose to research subjects and patients undergoing quantitative CT of the lungs. Several published works have emerged 46,47 demonstrating that IR methods reduce noise, while having non-linear effects on texture and low-contrast structures. The use of IR statistical and model-based methods will affect image noise and fine structures differently, which can have negative performance consequences for different types of quantitative imaging algorithms. Most IR methods allow for setting a strength level. Utilization of IR using low IR strength levels is generally advised. However, if that is not possible quantitative imaging researchers should take care to validate CT image quality is not negatively impacted for their COVID-19 clinical application before using CT images with high levels of iterative reconstruction.

#### 2.8. Reconstruction kernel

Reconstruction kernels can significantly alter or bias HU values, and these biases are not applied consistently across all three imaging dimensions. To avoid these issues for subsequent quantitative imaging analyses and algorithm development, it is recommended to use a reconstruction kernel that does not reduce spatial resolution (i.e., too "smooth") and does not introduce high levels of edge enhancement (i.e., too "sharp"). Ideally, scanning should be performed with the highest resolution reconstruction kernel available that does not result in high edge enhancement and/or noise (e.g., we do not recommend GE "LUNG", Siemens "B60f", or Philips "D"). Multiple methods exist to determine the level of edge enhancement in a CT image acquisition, including measurement with MTF analysis and other approaches. Several recommended kernel selections are listed in Table 1 below.

**Table 1**Recommended reconstruction kernels for quantitative CT COVID-19 applications.

CT scanner manufacturer	Models	Recommended reconstruction kernels
Canon/Toshiba General Electric Philips Siemens	All All Force All Others	FC05 STANDARD F, L Br40 B40, 140

#### 2.9. Follow-up scanning

When measuring quantitative change across temporally sequential CT scans, such as measuring disease progression or resolution in a COVID-19 patient, it is important to maintain the same or similar CT image quality over successive measurement time points. In an ideal setting, follow-up CT scanning would be performed on the same CT scanner with an acquisition protocol that is as identical to the baseline scan as possible. For quantitative results, it is particularly important to use the same reconstruction kernel, slice thickness, slice spacing, and dose. If possible, attempts should also be made to match FOV. Ideally, when there are multiple manufacturers and models of scanners at a single site, a standard quantitative chest protocol should be recorded into each scanner with settings already protocoled such that image quality (noise, resolution, etc.) is as equivalent as possible across scanners. Having COVID-19-dedicated scanners can help enforce the use of the same imaging protocols while at the same time limiting the risk of spreading infection to a single or single set of scanners.<sup>48</sup>

## 2.10. Retrospective studies using previously-acquired clinical CT scans

Diagnostic CT protocols used in the clinical setting frequently do not adhere to the technical specifications recommended here for prospectively designed studies. Slice thickness is often >1.25 mm. Reconstruction kernels may have been selected based on subjective visual preferences rather than quantitative accuracy. Implementation of radiation dose guidelines and use of automated exposure control methods may be variable. Multiple scanner models with different capabilities are typically available, and considerations other than those related to image quantification may determine the choice of which one to use with a particular patient.

Retrospective quantitative studies using CT scans previously obtained in the clinical setting therefore should be approached with rigorous assessment of the appropriateness of the scan acquisition and reconstruction techniques that were used. Some quantitative CT parameters may be assessable from images with >1.25 mm slice thickness, such as the volume and attenuation of regions or lesions much larger than the slice thickness; others may not, such as airway and vessel dimensions, or automated determination of lobar and segmental volumes. Studies relying on quantification of radiomics variables such as volume, shape, attenuation, and texture generally will require equivalence of technical scan parameters as an important factor for inclusion or exclusion; machine learning applications may permit greater variability in use of scans with different technical parameters if the data set is of adequate size.

QIBA is developing a set of CT image acquisition protocols for major CT scanner models that adhere to the above guidelines. More information on COVID-19 CT quantitative imaging protocols is available on the QIBA wiki page link referenced above.

## 2.11. Guidance on writing and reviewing CT imaging methods sections

A fast-paced research and development environment has emerged in response to the COVID-19 pandemic. This has pressured the research

community to accelerate the publication process, but despite the medical nature of this urgent situation, quality control of the publication process should not be compromised. Clinical publications must contribute to the literature in objective and meaningful ways, enabling other investigators to repeat, validate, and further advance the reported methodologies. Quantitative methods developed for the images used in one study might not generalize to images acquired in others, which can only be known if the technical parameters of the images used in the study are sufficiently reported. At a minimum, reported CT image acquisition parameters should include x-ray beam energy (kVp), tube current (mA), pitch, table feed direction, tube rotation time, collimation, reconstruction interval, in-plane pixel dimension, reconstruction algorithm, and scanner manufacturer and model along with information regarding contrast agent administration (if applicable) such as bolus volume, injection rate, and delay time. When any parameter is not uniform across all scans used in the study, the range and mean/median (as appropriate) of that parameter should be reported. Studies should report these parameters so that their impact on image quality and the underlying numeric data that constitute the image may be assessed and potentially reproduced by the reader.

Adherence to standard imaging protocols (and meeting defined minimum parameters) is useful for consistent clinical care and is essential to quantitative measurement as well as the training, testing, and validation of machine learning systems. Quality control of chest CT can be facilitated by a review of DICOM header fields to confirm that parameter selection was within the ranges recommended above to improve consistency of analysis and modeling of severity and response. More guidance on header fields is available publicly in the specific QIBA profiles for lung CT on the wiki page link referenced above. Moreover, complete and accurate reporting of the image acquisition parameters used in case reports or clinical or research studies submitted for publication is crucial for the further advancement of such methods and the eventual broad clinical adoption of the reported techniques. As reproducibility is a guiding principle of science, detailed image acquisition parameter reporting is a necessity. Authors are responsible for providing this information, but reviewers and journal editors represent an important check point for ensuring the information is complete.

#### 2.12. Software performance reporting

A wide variety of artificial intelligence approaches are being tested and promoted by different companies to automate and quantify the radiological findings consistent with COVID-19. Artificial intelligence techniques can be classified into three general categories: image processing (e.g., lung and lobar segmentation), image analysis (e.g., voxel-level tissue classification), and disease diagnosis directly from images without intermediate image analysis (e.g., diagnosis of COVID-19 directly from CT scans). AI-powered image processing is used to improve the results of traditional quantitative imaging techniques by making the underlying quantification workflow more accurate and robust. Voxel level tissue classification is used to help visualize and more accurately detect and quantify the extent and severity of disease. Direct AI-based diagnosis can be used to inform clinical decision making by computing personalized disease risk probabilities directly from the CT image or in conjunction with other data.

The majority of these methods rely on training datasets that have been previously adjudicated and annotated. Training data provenance is a fundamental element that requires a description of important training dataset characteristics: patient demographics, imaging protocol, outcome adjudication, and inclusion/exclusion criteria. Training provenance is essential to assess potential use cases for the proposed method and to enable comparisons across different approaches. It is of particular importance when employing direct disease classification, as the classification performance can be greatly influenced by the distribution of patient and imaging characteristics of the training data. <sup>50</sup> Ongoing efforts to create open databases that can facilitate the development of new

approaches should be adopted as much as possible. Several approaches rely on data augmentation techniques and transfer learning approaches that should be carefully described. A systematic report of the parameters used for training (optimizer parameters, number of epochs, and final model selection) are also important. The Food and Drug Administration recently requested comment on a document in which they proposed a framework for this review process. <sup>51</sup>

Validation and external replication are critical to assess the generalizability of the automated methods and the performance characteristics of data-driven approaches in a context different from that of the training. For example, a COVID-19 mortality risk prediction algorithm trained from data acquired in a country that used CT scanning heavily for COVID-19 screening may not be appropriate for use in country that only scans patients who have severe clinical features, as the underlying mortality risk distributions between the training and test cohorts are potentially very different. Information about the validation approaches that rely on resampling techniques such as cross-validation should provide details about the data selection process. Finally, external replication datasets should carefully describe patient demographics along with clinical and imaging characteristics.

#### 2.13. Open science

The numerous benefits of open science for improving and accelerating medical research have been well documented over the last decade. <sup>52,53</sup> Given the current urgency to rapidly develop and evaluate new quantitative imaging algorithms for COVID-19, it is particularly important that the global CT imaging community work toward making large, diverse, and high-quality imaging datasets openly available to the medical imaging research community.

Openly available COVID-19 imaging and metadata databases will allow numerous international research groups to immediately pursue research topics that use the open image data resources, thereby reducing development time and avoiding what are usually substantial costs needed to acquire image datasets. More importantly, numerous research groups will be able to operate in parallel on a common dataset, permitting a more direct comparison of algorithm results among research groups. Such direct comparison is a common feature of challenge initiatives where numerous algorithm development groups compete to achieve the best clinical application performance when running on the same dataset.

Large and openly available imaging and metadata databases will also be useful for COVID-19 clinical researchers pursuing data to investigate numerous potential questions regarding COVID-19 that CT lung imaging and thoracic image phenotype measurements are well suited to address. This includes investigations into new disease subtypes and relationships with other respiratory and cardiac diseases.

In addition, such open image databases allow for quantitative analysis required for multi-center research trials that ultimately can be collected for pooled analysis to accelerate our understanding of the evolution and natural history of this new viral pathogen. It is important to provide radiological image data in DICOM format so as to preserve image acquisition protocol and other information that is essential for understanding the quality and circumstances of the image data collected.

There are several initiatives underway throughout the world to create open image databases to accelerate COVID-19 imaging research. The RSNA has announced an initiative to build an open COVID-19 Imaging Data Repository, which will compile images and clinical data from the world to support COVID-19 research efforts. <sup>54</sup> Additional initiatives are also preparing to assemble and openly distribute longitudinal COVID-19 CT imaging databases. The ramp-up of multiple open COVID-19 CT imaging databases should accelerate the development of quantitative COVID-19 CT imaging algorithms to provide quantitative metrics for diagnosis and therapy.

#### 3. Conclusion

As global healthcare systems face unprecedented challenges to adequately care for massive numbers of COVID-19 patients, the clinical care community is starting to use quantitative COVID-19 applications to help improve diagnosis, assess stage, predict severity, and evaluate therapies. In addition, the quantitative CT lung imaging research community is rapidly developing quantitative CT imaging tools for COVID-19 clinical applications. Decades of CT lung imaging research has demonstrated that careful attention to CT acquisition protocols and image quality are critical to developing resilient quantitative imaging biomarkers and reliably determining their performance. Progress will be accelerated and fewer opportunities will be missed if quantitative CT imaging best practices advocated by quantitative lung imaging research communities are widely adopted. This is particularly important at the early stages of this global pandemic as the first studies, reports, and public imaging databases are disseminated to, and used by, global researchers. Important CT image acquisition considerations include use of elevated pitch scans to require less time for respiratory challenged patients to hold their breath, keeping respiratory level and CT image acquisition settings consistent over time, and selecting reconstruction kernels that minimize HU measurement bias. In addition, it is important that research publications follow recommended guidelines for specifying image acquisition methods in publications as this is critical to maintaining high scientific reproducibility. Global adoption of the quantitative imaging best practices outlined here and open dissemination of COVID-19 standardized CT imaging datasets will accelerate the development and validation of quantitative imaging biomarkers and potentially improve diagnosis and treatment of respiratory diseases.

#### Acknowledgement of additional collaborators

Kunwei Li, MD Chinese Academy of Medical Sciences Xueguo Liu, MD, PhD Fifth Affiliated Hospital of Sun Yat-sen Inversity

Ning Wu, MD Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College

Stephen Lam, MD BC Cancer Research Centre
Heidi Schmidt, MD Women's College Hospital
Edyta Szurowska, MD, PhD Medical University of Gdansk
Katarzyna Dziadziuszko, MD Medical University of Gdansk
Ante Marusic, PhD University of Zagreb

Dorith Shaham, MD Hebrew University-Hadassah School of Medicine

Gorka Bastarrika, MD Clinica Universidad de Navarra Nicholas Petrick, PhD Food and Drug Administration

#### References

- World Health Organization: Coronavirus disease (COVID-2019) situation reports [Internet]. World Health Organization. 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
- [2] Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA 2020;323(18):1843-4.
- [3] Bastos ML, Tavaziva G, Abidi SK, et al. Diagnostic accuracy of serological tests for covid-19: systematic review and meta-analysis. bmj 2020:370. British Medical Journal Publishing Group.
- [4] Nair A, Rodrigues J, Hare S, et al. A British Society of Thoracic Imaging statement: considerations in designing local imaging diagnostic algorithms for the COVID-19 pandemic. Clin Radiol 2020;75(5):329–34. Elsevier.
- Yang Q, Liu Q, Xu H, Lu H, Liu S, Li H, others. Imaging of Coronavirus Disease 2019: A Chinese expert consensus statement. Eur J Radiol. Elsevier; 2020;109008.
- [6] Ai T, Yang Z, Hou H, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology. 2020:200642.
- [7] Fang Y, Zhang H, Xie J, et al. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. Radiology 2020;200432. Radiological Society of North America.
- Dangis A, Gieraerts C, Bruecker YD, Janssen L, Valgaeren H, Obbels D, Gillis M, Ranst MV, Frans J, Demeyere A, others. Accuracy and reproducibility of low-dose submillisievert chest CT for the diagnosis of COVID-19. Radiology: Cardiothoracic Imaging. Radiological Society of North America; 2020;2(2):e200196.

[9] Schiaffino S, Tritella S, Cozzi A, et al. Diagnostic performance of chest x-ray for COVID-19 pneumonia during the SARS-CoV-2 pandemic in Lombardy, Italy. J Thorac Imaging 2020;35(4):W105–6. LWW.

- Radiology AC of, others. ACR recommendations for the use of chest radiography and computed tomography (CT) for suspected COVID-19 infection. 2020.
- Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, Schluger NW, Volpi A, Yim J-J, Martin IB, others. The Role of Chest Imaging in Patient Management during the COVID-19 Pandemic: A Multinational Consensus Statement from the Fleischner Society. Chest. Elsevier; 2020.
- Revel M-P, Parkar AP, Prosch H, Silva M, Sverzellati N, Gleeson F, Brady A, Radiology (ESR ES of, others. COVID-19 patients and the radiology department—advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). European Radiology. Nature Publishing Group; 2020-1
- [13] Bai HX, Hsieh B, Xiong Z, et al. Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT. Radiology. 2020;200823.
- Fan L, Li D, Xue H, Zhang L, Liu Z, Zhang B, Zhang L, Yang W, Xie B, Duan X, others. Progress and prospect on imaging diagnosis of COVID-19. Chinese Journal of Academic Radiology. Springer; 2020;1–10.
- [15] Shi H, Han X, Jiang N, et al. Radiological Findings From 81 Patients With COVID-19 Pneumonia in Wuhan, China: A Descriptive Study. The Lancet Infectious Diseases: Elsevier; 2020.
- [16] Shi H, Han X, Cao Y, Alwalid O, Zheng C. CT Screening for Early Diagnosis of SARS-CoV-2 Infection—Authors' Reply. The Lancet Infectious Diseases: Elsevier; 2020.
- [17] Wang Y, Dong C, Hu Y, et al. Temporal changes of CT findings in 90 patients with COVID-19 pneumonia: a longitudinal study. Radiology 2020;200843. Radiological Society of North America.
- Caruso D, Zerunian M, Polici M, Pucciarelli F, Polidori T, Rucci C, Guido G, Bracci B, de Dominicis C, Laghi A. Chest CT features of COVID-19 in Rome, Italy. Radiology. Radiological Society of North America; 2020;201237.
- [19] Wu J, Wu X, Zeng W, et al. Chest CT findings in patients with corona virus disease 2019 and its relationship with clinical features. Investig Radiol 2020:670. doi: 101097/BLI
- Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, Luo Y, Gao C, Zeng W. Chest CT Severity Score: An Imaging Tool for Assessing Severe COVID-19. Radiology: Cardiothoracic Imaging. Radiological Society of North America; 2020;2(2):e200047.
- Wen Z, Chi Y, Zhang L, Liu H, Du K, Li Z, Chen J, Cheng L, Wang D. Coronavirus Disease 2019: Initial Detection on Chest CT in a Retrospective Multicenter Study of 103 Chinese Subjects. Radiology: Cardiothoracic Imaging. Radiological Society of North America; 2020;2(2):e200092.
- [22] Li K, Fang Y, Li W, et al. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). Eur Radiol 2020:1–10. Springer.
- 23. Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, Henry TS, Kanne JP, Kligerman S, Ko JP, others. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA. Radiology: Cardiothoracic Imaging. Radiological Society of North America; 2020;2 (2):e200152.
- [24] Prokop M, van Everdingen W, van Rees Vellinga T, et al. CO-RADS-a categorical CT assessment scheme for patients with suspected COVID-19: definition and evaluation. Radiology 2020:201473. Radiological Society of North America.
- [25] LeCun Y, Bengio Y, Hinton G. Deep learning. Nature 2015;521(7553):436–44. Nat Publ Group.
- Li L, Qin L, Xu Z, Yin Y, Wang X, Kong B, Bai J, Lu Y, Fang Z, Song Q, others. Artificial Intelligence Distinguishes COVID-19 from Community Acquired Pneumonia on Chest CT. Radiology. 2020;200905.
- [27] Gozes O, Frid-Adar M, Greenspan H, et al. Rapid ai development cycle for the coronavirus (covid-19) pandemic: Initial results for automated detection & patient monitoring using deep learning ct image analysis. In: arXiv preprint arXiv: 200305037-2020
- 28. Wang S, Kang B, Ma J, Zeng X, Xiao M, Guo J, Cai M, Yang J, Li Y, Meng X, others. A deep learning algorithm using CT images to screen for Corona Virus Disease (COVID-19). medRxiv. Cold Spring Harbor Laboratory Press; 2020.
- Xu X, Jiang X, Ma C, Du P, Li X, Lv S, Yu L, Chen Y, Su J, Lang G, others. Deep learning system to screen coronavirus disease 2019 pneumonia. arXiv preprint arXiv:200209334. 2020.
- [30] Hurt B, Kligerman S, Hsiao A. Deep learning localization of pneumonia: 2019 coronavirus (COVID-19) outbreak. J Thorac Imaging 2020;35(3):W87–9. LWW.
- [31] Shan+ F, Gao+ Y, Wang J, et al. Lung infection quantification of covid-19 in ct
- images with deep learning. In: arXiv preprint arXiv:200304655; 2020.
   32. Wu Y, Xie Y, Wang X. Longitudinal CT findings in COVID-19 pneumonia: case presenting organizing pneumonia pattern. Radiology: Cardiothoracic Imaging. Radiological Society of North America; 2020;2(1):e200031.
- Huang L, Han R, Ai T, Yu P, Kang H, Tao Q, Xia L. Serial Quantitative Chest CT Assessment of COVID-19: Deep-Learning Approach. Radiology: Cardiothoracic Imaging. Radiological Society of North America; 2020;2(2):e200075.
- [34] Colombi D, Bodini FC, Petrini M, et al. Well-aerated lung on admitting chest CT to predict adverse outcome in COVID-19 pneumonia. Radiology 2020;201433. Radiological Society of North America.
- [35] Mei X, Lee H-C, Diao K, et al. Artificial intelligence-enabled rapid diagnosis of patients with COVID-19. Nat Med 2020:1-5. Nat Publ Group.
- 36. Quantitative Imaging Biomarker Alliance [Internet]. Quantitative Imaging Biomarker Alliance. Available from: https://qibawiki.rsna.org/index.php/Commi
- 37. Hersh CP, Washko GR, Estépar RSJ, Lutz S, Friedman PJ, Han MK, Hokanson JE, Judy PF, Lynch DA, Make BJ, others. Paired inspiratory-expiratory chest CT scans to

- assess for small airways disease in COPD. Respiratory research. Springer; 2013;14 (1):42.
- [38] Galbán CJ, Han MK, Boes JL, et al. Computed tomography–based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. Nat Med 2012;18(11):1711. Nat Publ Group.
- QIBA Lung Density Biomarker Committee. RSNA QIBA Lung Density Profile [Internet]. RSNA QIBA Lung Density Profile. Available from: https://qibawiki.rsna.org/index.php/Lung\_Density\_Biomarker\_Ctte.
- [40] Fain SB, Lynch DA, Hatt C. Invited commentary on "quantitative CT analysis of diffuse lung disease.". RadioGraphics 2020;40(2):E1–3. Radiological Society of North America.
- QIBA Small Lung Nodule Biomarker Committee. RSNA QIBA Small Lung Nodule Profile [Internet]. RSNA QIBA Small Lung Nodule Profile. Available from: htt ps://qibawiki.rsna.org/index.php/CT\_Small\_Lung\_Nodule\_Biomarker\_Ctte.
- Henschke CI, Yankelevitz DF, Yip R, Archer V, Zahlmann G, Krishnan K, Helba B, Avila R. Tumor volume measurement error using computed tomography imaging in a phase II clinical trial in lung cancer. Journal of Medical Imaging. International Society for Optics and Photonics; 2016;3(3):035505.
- [43] Mulshine JL, Gierada DS, Armato IIISG, et al. Role of the quantitative imaging biomarker alliance in optimizing ct for the evaluation of lung cancer screen-detected nodules. J Am Coll Radiol 2015;12(4):390-5. Elsevier.
- Rydzak CE, Armato SG, Avila RS, Mulshine JL, Yankelevitz DF, Gierada DS. Quality assurance and quantitative imaging biomarkers in low-dose CT lung cancer screening. The British Journal of Radiology. The British Institute of Radiology.; 2018;91(1090):20170401.
- [45] Heussel C, Kappes J, Hantusch R, et al. Contrast enhanced CT-scans are not comparable to non-enhanced scans in emphysema quantification. Eur J Radiol 2010;74(3):473–8. Elsevier.
- 46. Hammond E, Sloan C, Newell Jr JD, Sieren JP, Saylor M, Vidal C, Hogue S, De Stefano F, Sieren A, Hoffman EA, et al. Comparison of low-and ultralow-dose

- computed tomography protocols for quantitative lung and airway assessment. Med Phys. Wiley Online Library; 2017;44(9):4747–4757.
- [47] Rodriguez A, Ranallo FN, Judy PF, Fain SB. The effects of iterative reconstruction and kernel selection on quantitative computed tomography measures of lung density. Med Phys 2017;44(6):2267–80. Wiley Online Library.
- [48] Zanardo M, Monti CB, Cattaneo F, et al. Management of patients with suspected or confirmed COVID-19, in the radiology department. Radiography. In: Elsevier; 2020.
- [49] Mossa-Basha M, Medverd J, Linnau K, et al. Policies and guidelines for COVID-19 preparedness: experiences from the University of Washington. Radiology 2020; 201326. Radiological Society of North America.
- [50] Willemink MJ, Koszek WA, Hardell C, et al. Preparing medical imaging data for machine learning. Radiology 2020;295(1):4–15. Radiological Society of North America.
- 51. Food US, Administration D, others. Proposed Regulatory Framework for Modifications to Artificial Intelligence. Machine Learning (AI/ML)-based Software as a Medical Device (SaMD) Discussion Paper and Request for Feedback [Internet]. 2019;12. Available from: https://www.fda.gov/files/medical%20devices/published/US-FDA-Artificial-Intelligence-and-Machine-Learning-Discussion-Paper.pdf.
- [52] Huston P, Edge V, Bernier E. Open Science/Open Data: Reaping the benefits of Open Data in Public Health. Canada Communicable Disease Report45(11). Public Health Agency of Canada; 2019. p. 252.
- Ibáñez L, Ávila R, Aylward S. Open source and open science: how it is changing the medical imaging community. 3rd IEEE International Symposium on Biomedical Imaging: Nano to Macro, 2006. IEEE; 2006. p. 690–693.
- Radiological Society of North America: COVID-19 Resources [Internet]. Radiological Society of North America: COVID-19 Resources. Available from: https://www.rsna. org/covid-19.